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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,096	03/22/2004	**Allan Svendsen**	10321.200-US	2911

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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,096	SVENDSEN ET AL.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-57 and 59-63* is/are pending in the application.

4a) Of the above claim(s) *40-55* is/are withdrawn from consideration.

5)☒ Claim(s) *62* is/are allowed.

6)☒ Claim(s) *56,57,59-61 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's substitute specification and amended sequence listing filed with the Response of 16 April 2007 have been reviewed and it is agreed that they introduce no new matter. They are APPROVED and the amendments incorporated in the substitute specification overcome the objection of record of the specification. While the amendments of claims 56, 57, and 59 in the Response filed 16 April 2007 overcome the objection of record to the claims, and the newly submitted claims 60-93 do not introduce new matter to the disclosure, they necessitate new objections to the claims, and new rejections of the claims stated below. Some aspects of the rejection of record of claims herein under the second paragraph of 35 U.S.C. § 112 are maintained where the amendments do not address all issues raised, and the new claim 63 recapitulates an indefinite form of description removed by the amendment of 16 April 2007 from the earlier-presented claims. As claim 58 was cancelled at Applicant's request, claims 40-57 and 59-63 remain in the application, of which claims 56, 57, and 59-63 are examined below.

Election/Restrictions

Applicant's election **with** traverse at page 10 of the Response of 16 April 2007 of the invention of Group 2, now represented by claims 56, 57, and 59-63 herein, wherein the species of variant JP 170-like subtilase elected has a modification at the position corresponding to S193 in the amino sequence of SEQ ID NO:1, 56, 57, and 59-63 is acknowledged. The traversal is on the ground(s) that search and examination of two or more Groups of inventions would not "be a burden". This is not found persuasive because "a serious burden on the examiner may be *prima facie* shown . . . by . . . separate classification", MPEP § 803, and the restriction requirement in the communication mailed 20 October 2007 stated the separate classifications of each of the inventions of Groups 1 and 2, explained why each Group was distinct from the other and Applicant does not traverse the classifications provided. The requirement as to restriction among Groups 1 and 2 is still deemed proper and is therefore made FINAL.

Objections to the Claims- 35 USC § 112

Claim 63 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 63 states a dependency from claim 61 which, in turn, states a dependency from claim 57. While every position modified by an amino acid substitution in claim 61 is previously recited in claim 57, only one site - 47 - identified for an amino acid substitution in claim 63 is recited in claim 57, but the insertion and the other substitutions recited in claim 63 find no antecedent basis in the claims 57 and 61. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or

rewrite the claim in independent form. Dependency from claim 62 is, however, logical thus claim 63 is not withdrawn from consideration in order to expedite prosecution in view of the clear opportunity for changing its dependency to resolve this issue.

Claims 57 and 61 are objected to because of the following informalities: Claim 57 first recites "wherein modifications are made in at least one position", erroneously suggesting that a recited position may undergo multiple modifications, then thrice recites "wherein the at least one position . . . **are** selected (emphasis supplied)" but the singular form of the verb "to be" is required. In claim 61 has a non-sequential ordering of the positions for substitution and a combination therein, reducing the ability of the public to quickly envisage the intended subject matter. Appropriate correction is required, e.g., reordering the recitation of positions thus: "S193Q,Y; D196N; H200D,N; N390D; N391D; W392S,N,Q; and G394N,Q,F,Y,S. There is no need to repeat the alternative substitution, "H200D,N", together with "+D169" where recitation of "comprises at least one of the modifications" includes all combinations of recited modifications. If Applicant desires to set forth the two specific combinations, a separate, dependent, claim is the appropriate place to state, "wherein the modification is H200D+D196N or H200N+D196N".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56, 57 and 59, and the new claims 60-63, are rejected, essentially for reasons of record, under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 16 April 2007 have been fully considered but they are not persuasive. Applicant suggests at pages 11-12 of Remarks filed 16 April 2007 that the claim amendments requiring 90% "similarity", which is narrowly construed as "identity" for the sake of this argument, to the amino acid sequence of SEQ ID NO:1 removes the basis for the rejection of record. If only SEQ ID NO:1 is considered as the starting point for modification, the claims permit as many as 43 (10% of 433 amino acid positions) concurrent modifications. Claim 62 by describes one such concurrent modification - a deletion of, then replacement of, four contiguous amino acid positions - yet admits as many as 40 further modifications elsewhere. The claim amendments do not resolve the issue of whether the claims are intended to describe a "variant JP170 type subtilase" comprising as many as 43 amino acid substitutions that is itself already a "variant" subtilase because it differs, before making any claimed modification, from the amino

acid sequence of SEQ ID NO:1 by virtue of being a "JP170 type" subtilase. In addition, claims 56, 57 and 60-83 permit modifications at other, non-specified, positions, beyond those recited in the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification fails to describe the modification of a "JP170 type" subtilase, or even the JP170 subtilase having the amino acid sequence set forth in SEQ ID NO:1, to the extent permitted by the limitation "90% similarity". Neither does it furnish relevant identifying characteristics of "variant" subtilases that concurrently diverge at as many as 43 amino acid positions from the sequence set forth in SEQ ID NO:1, nor provide characteristics permitting a correlation between the undisclosed structures of "variant" subtilases among the members of the genus of claims 56. 57, and 59-63 wherein the amino acid sequence of SEQ ID NO:1 is modified concurrently at as many as 43 amino acid positions. The rejection of record is therefore maintained.

Claims 56, 57, and 59 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a variant JP170 subtilase wherein the variant subtilase has an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:1 due to an amino acid sequence modification at one or more of the positions now recited in claims 57 and 59, does not reasonably provide enablement for the preparation and use of a variant subtilase having 43 or more amino acid sequence modifications in the amino acid sequence set forth in SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 16 April 2007 have been fully considered but they are not persuasive. Applicant suggests at pages 12-13 of Remarks filed 16 April 2007 that the claim amendments requiring 90% "similarity", now narrowly construed as "identity" for the sake of this argument, to the amino acid sequence of SEQ ID NO:1 removes the basis for the rejection of record. As noted above, the claims reach as many as 43 acid substitutions, additions, or deletions in generic proteins, as well as in the mature JP170 subtilase of SEQ IA NO:1 and only claim 59 is limited to a closed set of positions for substitution. Yet the specification can identify specific amino acid substituents for only 14 of the more than 100 amino acid positions in SEQ ID NO:1 recited in claims, and the claims do not require that the unspecified substituents, or that addition or deletion of amino acids, at any of the further positions have any particular result upon modification even of the disclosed JP170 subtilase of SEQ ID NO:1. At most, the rejected claims require only that the resulting modified, molecule function as a subtilase, i.e., can cleave covalent bonds between some amino acids, but mere sequence perturbation cannot enable the design and preparation of divergent subtilases and provide the public with variant subtilases that retain proteolytic activity. The rejection of record is maintained because:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the reference JP170 subtilase having the amino acid sequence of SEQ ID NO:1 to the extent permitted in the rejected claims,

b) the specification lacks working examples wherein the amino acid sequence of the reference JP170 subtilase having the amino acid sequence of SEQ ID NO:1, is altered to the extent permitted in the rejected claims,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of mature subtilases having amino acid sequences of about 344 amino acids represented by the reference amino acid sequence of SEQ ID NO:1, have had even a few amino acid positions identified for concurrent modification.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56, 57, 59 are rejected, and claims 60-63 are now rejected, essentially for reasons of record, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 16 April 2007 have been fully considered but they are not persuasive. Applicant suggests that claim amendments of 16 April 2007 make the claims clear. Yet claims 56 and 57 remain indefinite, as well as the new claims 60 and 61 depending therefrom, because they fail to state any fixed point, or coordinate, for measuring the subject matter indicated by the phrase "modification in an amino acid residue in a position located at a distance of 10Å (6Å) or less to". Claim 56 does not state any number of ion binding states, thus may reach more than the three indicated in claim 57, and claim 57 would, if each recited position were taken as a focal point, provide over 50 foci. Claim 62 is included in this rejection where it indicates that a further ion binding site is also available for measuring a 10Å radius, presumably a "weak" site since the claim suggests a process for making a site a "Strong" ion binding site. If the specification provides any basis for establishing amino acid positions within a 10Å radius, or a 6Å radius, from (a) definite position(s) – four are now indicated in the pending claims – the claims have yet to recite such foci and such a basis, thus the public and artisan seeking to ascertain the metes and bounds of the claimed subject matter cannot know which positions, that might advantageously be described according to their correspondence with the amino acid sequence of SEQ ID NO:1, see below, embraced by the claims.

The new claim 63 is indefinite because it states the terms "optionally . . . and/or", which leaves it unclear whether limitation(s) following these phrases are part of the claimed invention. See MPEP § 2173.05(d). In this national forum, the proper form for presenting multiple, related, subject matters in patent claims is to provide claims of different scope where (an) initial claim(s) describe(s) only the subject matter having the broadest scope now present in each of the rejected claims and is followed by one or more dependent claim(s) that refer(s) back to the initial

claim and that describe(s) subject matter(s) of progressively lesser scope that now follow the terms "optionally" in claim 63. It is again suggested that providing a separate, dependent, claim reciting a subset of the currently-recited "options" that introduce a multiple scope in the same claim will overcome this aspect of the rejection.

Claims 57 and 59 remain indefinite, and the new claims 61-63 are similarly indefinite because, even though they now state a sequence identifier for the amino acid sequence of a reference subtilase, the claims may be considered to describe multiple starting subtilases that may differ by as much 10% from SEQ ID NO:1 in sequence "similarity", a term that might imply "identity", before modification, yet the claims fail to require that particular, or intended, positions be modified. While a particular amino acid sequence, SEQ ID NO:1, is recited in the claims they cannot identify the context in which the designated positions occur in order that an additional amino acid, or lack thereof, occurring elsewhere in a particular protease amino acid sequence create no ambiguity in interpreting the claims. This rejection may be overcome by amending claims 57, 59 and 62 to insert a further clause that states, "wherein said positions correspond to the amino acid positions of SEQ ID NO:1".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 56, 57, and 59-61 are rejected under 35 USC § 102(a) as being anticipated by Hatada et al., EP 1 209 233, made of record with Applicant's Information Disclosure Statement [IDS].

This is a new ground of rejection thus this communication is not made final. The amino acid sequence of the alkaline protease of SEQ ID NO:1 of Hatada et al. '233 is identical to the amino acid sequence of the JP170 protease set forth in SEQ ID NO:1 herein, thus Hatada et al. '233 anticipate the invention of claims 56, 57, and 59-61 in their disclosures at pages 2-4 in paragraphs 6, 7, 10, 13, and 16-18 wherein the amino acids at positions 193, 195, 342, and 369 are replaced with a different amino acid. Hatada et al. '233 more particularly disclose the elected invention of claim 61 in clause (f) of paragraph 16 at lines 12-14 of page 4 wherein the serine at position 193 of SEQ ID NO:1 herein is substituted with glutamine or tyrosine.

Claims 56, 57, and 59-61 are rejected under 35 USC § 102(e) as being anticipated by Hatada et al., US 6,803,222, made of record herewith.

This is a new ground of rejection thus this communication is not made final. The amino acid sequence of the alkaline protease of SEQ ID NO:1 of Hatada et al. '222 is identical to the amino acid sequence of the JP170 protease set forth in SEQ ID NO:1 herein, thus Hatada et al. 'anticipate the invention of claims 56, 57, and 59-61 in their disclosures from col. 1, line 49, through col. 7, line 52, and in Figures 1-3, particularly in Figure 2, wherein the amino acids at positions 193, 195, 342, and 369 are replaced with a different amino acid. Hatada et al. '222 more particularly disclose the elected invention of claim 61 at, e.g., col. 2, lines 18-25, wherein the serine at position 193 of SEQ ID NO:1 herein is substituted with glutamine or tyrosine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 59 remains rejected for reasons of record under 35 U.S.C. § 103(a) as being unpatentable over Sloma et al., '701, in view of Zukowski et al., '705, both of record.

Applicant's arguments filed 16 April 2007 have been fully considered but they are not persuasive. Applicant suggests at page 13 of the remarks accompanying the claim amendment that Sloma et al., who teach the amino acid sequence of the mature Bacillus JP170 subtilase, would have indicate where its amino acid sequence, which is the SEQ ID NO:1 herein, should advantageously before an artisan at the time the invention was made would have considered the application of the teachings of Zukowski to be appropriate. It is first noted that Applicant argues limitations not present in claim 59, which is an independent claim and does not require that any recited position for modification be present in an ion binding site. Regardless of whether or not a three-dimensional structure of the JP170 subtilase is determined after it has been crystallized, Sloma et al. teach that amino acid substitutions should be made in the JP170 subtilase for the same kinds of reasons, well-known in the prior art, that amino acid substitutions were made in other subtilases, e.g., modifying the thermostability, oxidative stability, specific activity, and pH optimum of the native subtilase. See col. 5 at lines 8-14. Thus the artisan would indeed have considered the application of the teachings of Zukowski et al. to the teaching of Sloma et al. to be appropriate where Zukowski et al. go beyond teaching certain positions within a calcium ion binding site that may be modified to reinforce calcium binding to produce increased thermal stability of another subtilase, see columns 7 and 8, to further teach that other

amino acid substitutions at positions can increase the stability of a modified subtilase over that of the subtilase before modification for reasons unrelated to ion binding. Hatada et al. '222 is cited as evidence that resolution of the three-dimensional structure of the JP170 protease was unnecessary to a determination of where to make worthwhile, stabilizing, modifications of the amino acid set forth in SEQ ID NO:1. Zukowski et al. teach that the stability of any subtilase is improved by substituting isoleucine, serine, valine, cysteine, glutamine, or threonine for either an asparagine or a glycine within an asparagine-glycine pair. See, col. 6 line 37, through line 22, and claims 1, 2, and 10-16. Zukowski et al. also teach that substituting an alanine or leucine for a methionine in a subtilase, whether within or outside the active site region, provides an improved oxidative stability in the modified subtilase. See, col. 7, lines 23-47, and claims 1, 2, 6, 7 and 16. "[Recognition that] a design step well [was] within the grasp of a person of ordinary skill in the relevant art[,] arguments, and the record, [may] demonstrate that [a] claim . . . is obvious." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1401 (U.S. 2007).

Absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Zukowski et al. to the JP170 subtilase amino acid sequence taught by Sloma et al. to make a variant of claim 59 by replacing a glycine at positions 67 and/or 376 of the JP170 subtilase, or an asparagine at positions 134 and/or 375 of the JP170 subtilase, because Zukowski et al. teach that abolishing the occurrence of an asparagine-glycine pair any subtilase by making such amino acid modifications provides a subtilase variant with increased stability. Absent evidence to the contrary, it would also have obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Zukowski et al. to the teachings of Sloma et al. to the JP170 subtilase amino acid sequence taught by Sloma et al. to make a variant of claim 59 by replacing one of more of the methionines at positions 42, 97, and 153 of the mature JP170 subtilase where Zukowski et al. teach that replacing methionines in a subtilase wherever they occur provides a subtilase variant with increased oxidative stability. Such an artisan would have had a reasonable expectation of success in making such substitutions because Sloma et al. suggest that the mature JP170 subtilase can advantageously be modified according to teachings of the prior art to achieve the purposes taught in the prior art. "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1398 (U.S. 2007). The rejection of record is therefore sustained.

Conclusion

While claim 63 is subject to an objection above, and both of claims 62 and 63 are subject to rejections above under 35 U.S.C. § 112, the subject matter of claims 62 and 63 is free of the prior art of record herein because it is clear that knowledge of the three-dimensional structure of a subtilase, or a close sequence homologue, is a prerequisite to the analysis of the contribution of any particular peptide region to an ion binding site, and that a modification of such a peptide region must be tested to confirm the analysis. See col. 2, lines 53-67 of Svendsen et al., US 7,294,499, made of record herewith.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashed/
Nashaat T. Nashed, Ph.D.
Supervisory Primary Examiner
Art Unit 1652

William W. Moore
22 February 2008